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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,371	03/26/1999	DAVID LANE	4-20937/A/PC	8832

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EXAMINER	
ZARA, JANE J	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/214,371	LANE ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-36,38-42 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33,35,36,38-42 and 52* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 8-13-04.

Claims 27-36, 38-42 and 52 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, because the specification, while being enabling for a method of inhibiting DM2 protein binding to p53 in vitro comprising contacting DM2 protein with a polypeptide comprising SEQ ID Nos: 4, 6-8 and 10-14, does not reasonably provide enablement for a method of inhibiting the binding of DM2 and p53 in vivo comprising contacting DM2 protein with a polypeptide comprising SEQ ID Nos: 4, 6-8 and 10-14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is repeated for the same reasons of record set forth in the Office actions mailed 5-23-03 and 2-25-04.

Applicant's arguments filed 8-13-04 have been fully considered but they are not persuasive. Applicants argue that the invention is enabled for the full scope claimed and that the Examiner has the initial burden of challenging a presumptively enabling disclosure, and that the conclusory statements of the Examiner do not provide acceptable evidence or reasoning for a lack of enablement. The claimed invention is drawn to a method of inhibiting DM2 protein binding to p53 in vitro and in vivo comprising administration of a peptide comprising SEQ ID NO: 4. The instant disclosure teaches methods of inhibiting DM2 binding to p53 in vitro comprising the administration of peptides (e.g. using Elisa assays). The ability to inhibit peptide binding in vitro is not representative of the ability to inhibit protein interactions in vivo. Contrary to Applicants' assertions, it requires more than routine experimentation to accomplish sufficient peptide delivery into target cells, and into desired subcellular organelles, to inhibit binding in vivo. The ability of polypeptides to penetrate cellular membranes requires exceptional characteristics, and examples of molecules involved in the process of membrane transport through cells include antennapedia, transportan and Herpes virus structural protein, all of which are discussed in more detail below. Obtaining sufficient peptide delivery to target cells in vivo to cause a desired physiological response (such as inhibiting peptide binding or protein-protein interactions) is an unpredictable endeavor and cellular delivery of peptides and proteins has been a limiting factor repeatedly addressed by investigators in the field.

The following references are cited herein to illustrate that the delivery and adequate uptake of polypeptides by a target cell in vitro or in vivo is generally an energy

dependent process and requires the presence of specific proteins - with exceptional characteristics - that serve as receptors and/or channels. This process of active cellular uptake is discussed in the context of exemplary and exceptional molecular entities that are well known in the art to act as peptide or protein transporters for target cells.

Derossi et al, for example, teach the ability of antennapedia homeodomain to translocate through biological membranes, which is an unusual capability for a protein to be able to do. The ability for a polypeptide to translocate through cellular membranes is highly sequence dependent, and illustrates that delivery of polypeptides to target cells, allowing sufficient uptake by target cells in vitro or in vivo, is a rate limiting step for cell targeting and entry of most polypeptides (see D. Derossi et al. J. Biol. Chem. 269(14): 10,444-10,450, especially the abstract on p. 10,444, last paragraph of the introduction on p. 10,444; first full paragraph on p. 10,450: "Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria... Passage through these intracellular membranes is energy-dependent and requires the presence of specific proteins that serve as receptors and/or channels. However, even in this rather well studied system, the actual mechanism of importation is not yet completely understood."

For specific requirements of other, specialized polypeptides involved in cellular membrane penetration, see M. Pooga et al. FASEB J. 12: 67-77 for a discussion of the remarkable properties of transportan; see also G. Elliott et al, Cell 88: 223-233 for the distinguishing features of Herpes virus structural protein and its role in intercellular

trafficking). Consistent with the view held by these authors, the instant disclosure also addresses ways of overcoming the hurdle of sufficient peptide delivery to target cells. On page 36, example 10, first sentence, the instant disclosure states that "[t]o improve the intracellular stability and facilitate cellular uptake of the peptides..., peptide binding elements may be constructed..." And on page 39, first paragraph, the instant disclosure teaches the intranuclear injection of various polypeptides in order to achieve sufficient and appropriate subcellular delivery of them. The examples provided in the art (above) and the instant specification together provide acceptable evidence and reasoning to conclude that the in vivo targeting, delivery and successful inhibition of DM2 binding to p53 comprising the administration of peptides is highly unpredictable and require undue experimentation beyond that provided in the prior art and in the instant disclosure.

Applicants also argue that claim 1 issued in a prior patent (USPN 6,153,391) reads on both in vivo and in vitro methods and therefore enables the instantly claimed invention. The determination of enablement for the instant application is the issue before us, not the prosecution history of an unrelated, previously issued patent. The determination of enablement is therefore based on the facts before us. And based on the facts before us regarding this application, the instant disclosure teaches methods of inhibiting DM2 binding to p53 in vitro using Elisa assays of cellular extracts. No intracellular or appropriate subcellular delivery of peptides (in vitro or in vivo) have been provided, and further whereby DM2 binding to p 53 has been inhibited in target cells in vitro or in vivo. The results obtained using cellular extracts in competitive binding assays are not representative or correlative of the ability to inhibit protein binding in a

target cell in vitro or in vivo. So, contrary to Applicants' assertions, one of skill in the art would reasonably conclude that the instant invention is not enabled for the full scope claimed, which encompasses the ability to inhibit DM2 and p53 binding in a target cell in vitro or in vivo following the administration of the claimed peptides.

New Rejections Necessitated by Amendment

DETAILED ACTION

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 27, 28, 33, 35, 36, 38-42 and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by Bottger et al.

Bottger et al (Oncogene 13: 2141-2147, 1996) teach the in vitro inhibition of DM2 and p53 binding comprising the administration of a composition comprising a pharmaceutically acceptable diluent (water) and a peptide of SEQ ID NO: 4 or SEQ ID NO: 11, (and further comprising the amino acid components set forth in claims 39, 40 and 42) (see the abstract and introduction on p. 2141; Table 1 on p. 2142, and figure 5 on p. 2144).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al as applied to claims 27 and 28 above, and further in view of Dower et al.

The claims are drawn to a peptide that binds to DM2 and comprises the formula of SEQ IDNO: 4, which peptide is optionally a cyclic peptide, comprises a cyclic lactam or a disulfide bond, or is optionally coupled to a biotin moiety.

Bottger et al is relied upon as cited in the 102 rejection above. Bottger et al do not teach peptides coupled to biotin moieties, nor cyclic peptides, nor peptides comprising a cyclic lactam or a disulfide bond.

Dower et al (USPN 6,121,238) teach the cyclic peptides (col. 4, lines 20-39), peptides comprising cyclic lactams (col. 31, line 56-col. 32, line 3), disulfide bonds (col. 37, lines 32-67), and peptides optionally coupled to biotin moieties (figure 1A).

It would have been obvious to one of ordinary skill in the art to design cyclic peptides, peptides comprising cyclic lactams or disulfide bonds, and/or optionally

comprising biotin because all of these structures were all well known in the art at the time the invention was made, as taught by Bottger et al, and cyclic peptides, peptides comprising cyclic lactams or disulfide bonds were well known in the art to exhibit improved target binding and enhanced binding specificity because of their ability to introduce structural constraints onto the peptides, as taught previously by Bottger et al. Furthermore, the incorporation of biotin onto peptides was well known in the art, and one would have been motivated to incorporate biotin onto a peptide for several reasons, including as a linker to bind an avidin moeitiy for labeling purposes, affinity purification, as a separation or enrichment technique or to couple other avidin labeled entities to the peptides. One of ordinary skill in the art would have expected cyclic peptides or peptides comprising cyclic lactams or disulfide bonds to be structurally constrained and exhibit better binding affinity for binding site (e.g. as a competitive inhibitor of protein binding) and one would expect biotin labeled peptides to have a high affinity for avidin. One of ordinary skill in the art would have expected to retain and/or enhance the binding properties of the peptide following cyclization of binding peptides or incorporation of biotin, and incorporating these modifications and testing modified peptides for their ability to retain binding function was a routine matter in the art, as illustrated previously by the teachings of Bottger et al and Dower et al. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27, 28, 32-40 and 52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read broadly on peptides which comprise an amino acid motif comprising at least the eight consecutive amino acids of the formula of SEQ ID NO: 4. Since the size of peptides is not precisely described or indicated in the instant disclosure, and since the term *comprising* reads broadly to encompass larger polypeptides including full length proteins, the breadth of the claims is therefore interpreted to encompass full length polypeptides comprising the motif of SEQ ID NO: 4, which include products of nature (e.g. inserting –isolated—before "peptide" would be remedial).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
10-26-04

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